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Review Article

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A Brief Review of the Synthesis and Therapeutic Potential of 1,10-Phenanthroline Heterocycle

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Abstract The 1,10-phenanthroline tricycle and its derivatives are of great interest in medicinal chemistry. Some years several research papers have been published on the 1,10-phenanthroline core alone or complexed with various metals. Researchers have explored new approaches to functionalize the 1,10-phenanthroline motif in order to obtain less toxic potential drug candidates without adding additional metals. This research has shown that the 1,10-phenanthroline tricycle and its derivatives possess important antimalarial, antimicrobial, antitubercular, antifungal, antiviral, anti-inflammatory, anticancer and antioxidant properties. This review of the literature will discuss the different methods of construction of the 1,10-phenanthroline tricycle as well as the therapeutic potential of 1,10-phenanthroline derivatives not coupled to transition metals.

Keywords 1,10-phenanthroline, synthesis, therapeutic potentiality, antimalarial, antitubercular, antibacterial

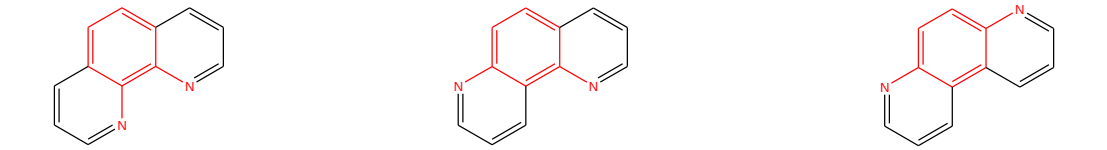
1. Introduction

1,10-phenanthroline and its derivatives are compounds with excellent intercalation capacity with DNA base pairs [1-3]. In addition, the 1,10-nitrogen arrangement favors a non-specific inhibition of metalloproteins, which increases their toxicity [4-6]. As this toxicity limits the therapeutic use of 1,10-phenanthroline derivatives, various complexes with transition metals have been developed to reduce this toxicity [7-11]. In addition, complexes of 1,10-phenanthroline with transition metals most often lead to incomplete intercalation of DNA base pairs because the nitrogen atoms required for intercalation are engaged in coordination bonding with the transition metals, which could result in decreased biological activities [12, 13]. Efforts to chemically modulate 1,10-phenanthroline derivatives to reduce toxicity without the addition of transition metals seems to be an alternative solution. While for transition metal-coupled 1,10-phenanthrolinone derivatives, there are several reviews [14-19], this is not the case for metal-uncoupled derivatives. This is why we have set ourselves the objective of listing the main methods of 1,10-phenanthroline tricycle edification as well as the therapeutic potentialities of non-metal coupled 1,10-phenanthroline derivatives.

2. Chemistry of 1,10-phenanthroline

Phenanthrolines (**Figure 1**) are tricyclic compounds belonging to the chemical group of diazaphenanthrenes. Depending on the position of the nitrogen atoms in the tricyclic ring, three isomers are distinguished: 1,10-diazaphenanthrene, 1,7-diazaphenanthrene and 4,7-diazaphenanthrene. These isomers are also referred to as ortho-phenanthroline for the 1,10-diazaphenanthrene isomer, meta-phenanthroline for the 1,7-diazaphenanthrene isomer

and para-phenanthroline for the 4,7-diazaphenanthrene isomer [20]. The prefixes ortho, meta and para are related to the arrangement of the two amine functions of the phenylenediamine used as starting material in the synthesis of diazaphenanthrenes. Thus, ortho phenanthroline, meta-phenanthroline and para-phenanthroline are derived from orthophenylenediamine, meta phenylenediamine and para phenylenediamine respectively [21].



1,10-diazaphénanthrène (*Ortho* phenanthroline) (1,10-phénanthroline)

1,7-diazaphénanthrène (*Méta* phenanthroline) (1,7-phénanthroline)

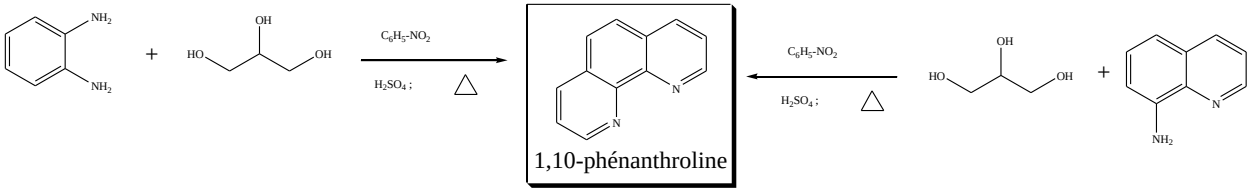
4,7-diazaphénanthrène (*Para* phenanthroline) (4,7-phénanthroline)

Figure 1: Chemical structure of diazaphenanthrene

Historically, the first 1,10-diazaphenanthrene derivative was prepared in 1889 by Gerdeissen. It is a white solid, the monohydrate form of which has a melting point of 117 °C. It is soluble in most common organic solvents [22]. Various methods of tricyclic 1,10-phenanthroline construction have been described in the literature but all these methods have in common the use of orthophenylenediamine or 8-aminoquinoline as starting material.

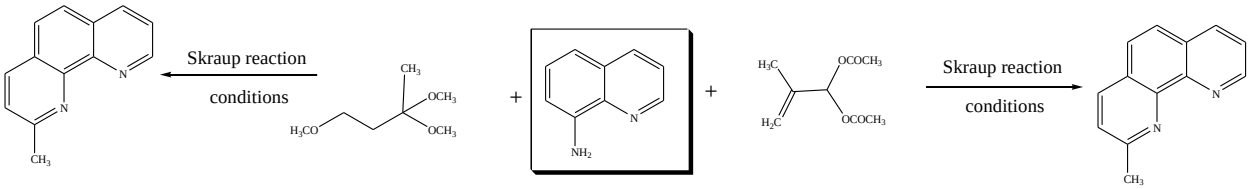
2.1. Skraup type reaction

The Skraup reaction is a chemical reaction for the synthesis of quinolines discovered in 1880 by Zdenko Skraup. It consists of reacting aniline with glycerol in the presence of sulfuric acid and an oxidizing agent such as nitrobenzene at 100 °C [23-25]. Later, Skraup's reaction conditions were applied to orthophenylenediamine or 8-aminoquinoline to build the 1,10-phenanthroline tricycle. Thus, Blau reported in 1898, the synthesis of 1,10-phenanthroline (Scheme 1) from orthophenylenediamine and glycerol by a double Skraup reaction in the presence of nitrobenzene [26]. A variant of this method has been reported in a patent, advocating the catalytic addition of copper salts and the use of meta-nitrobenzenesulfonic acid as an oxidizing agent to improve yields [27]. Nevertheless, the synthesis of 1,10-phenanthroline by double Skraup reaction on ortho-phenylenediamine leads to yields of 40% or less [28-30]. The first 1,10-phenanthroline, more precisely 2-methyl-1,10-phenanthroline, was prepared in 1889 by Gerdeissen, by applying the Skraup reaction conditions to 8-aminoquinoline and glycerol [22]. Again, there are several variants but the best yields of 65% were obtained by cyclization in the presence of copper salts [27,31].



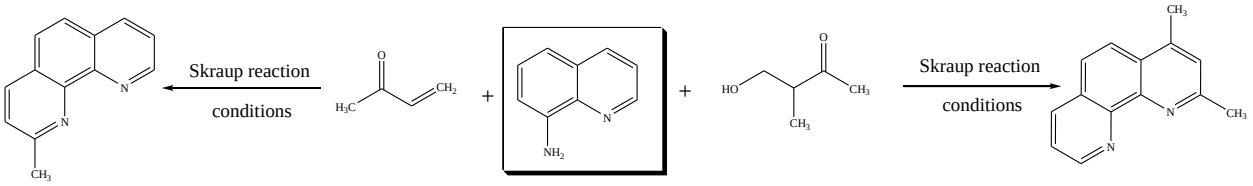
Scheme 1: Synthesis of 1,10-phenanthroline from ortho-phenylenediamine and 8-aminoquinoline

Applying Skraup's reaction conditions, CASE and coworkers obtained methylated or polymethylated derivatives of 1,10-phenanthroline (**Scheme 2**) by condensation of 8-aminoquinoline with α,β-unsaturated aldehyde diacetates or the ketals [32-34].



Scheme 2: Synthesis of methylated or polymethylated derivatives of 1,10-phenanthroline from α,β-unsaturated aldehyde diacetates or ketals

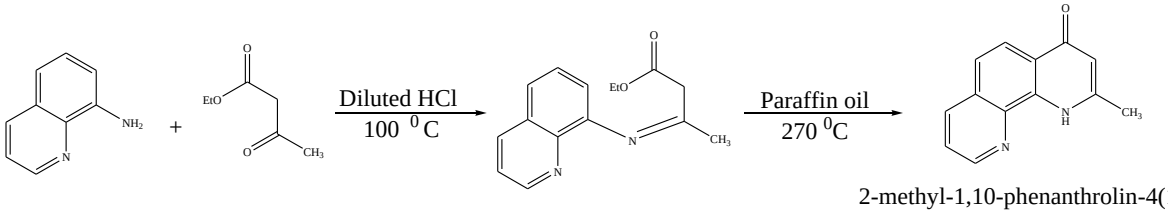
Furthermore, by replacing the aldehyde derivatives with other carbonylated α,β-unsaturated ketone or ceto-alcohol derivatives, this team also obtained methylated or polymethylated derivatives of 1,10-phenanthroline (**Scheme 3**) under Skraup conditions [32-34].



Scheme 3: Synthesis of methylated or polymethylated derivatives of 1,10-phenanthroline from α,β-unsaturated ketones or ceto alcohols

2.2. Conrad-Limpach type reactions

Like the Skraup reaction this reaction was developed the synthesis of quinolines. It consists in reacting a primary aromatic amine with a β-ketoester to lead to the 4-hydroxy quinoline via an enamine intermediate [35, 36]. The application of the Conrad-Limpach synthesis to 8-aminoquinoline allowed by Hazelwood and collaborators to obtain a 1,10-phenanthrolinone derivative (**Scheme 4**) more exactly the 2-methyl-1,10-phenanthrolin-4(1H)-one [37].

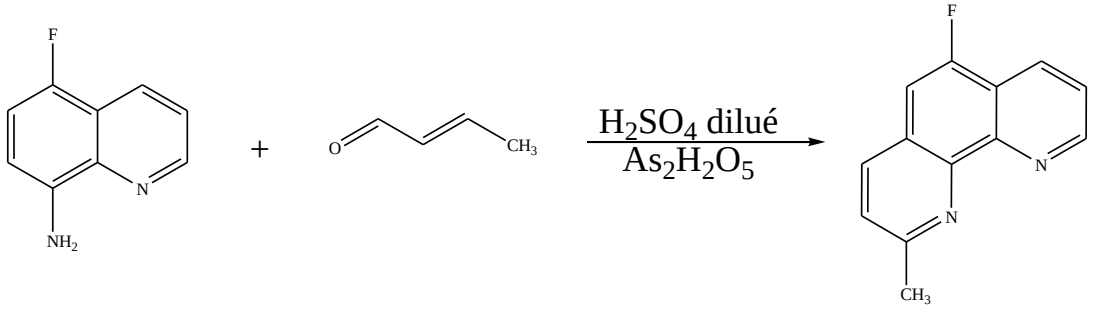


2-methyl-1,10-phenanthrolin-4(1*H*)-one

Scheme 4: Edification of tricycle1,10-phenanthrolinone by the Conrad-Limpach method

2.3. The Doebner-Von Miller type reaction

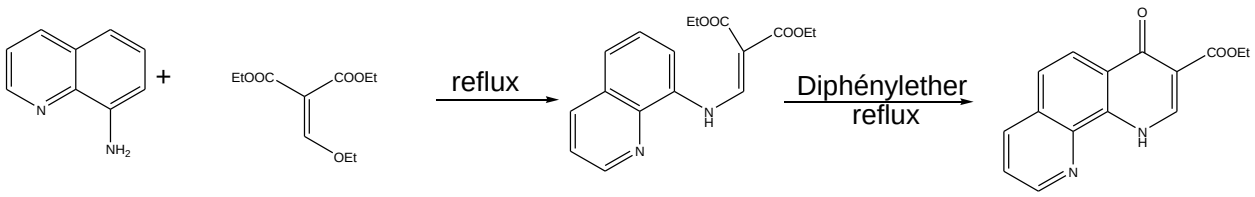
This reaction is a variant of the Skraup synthesis of quinolines, it consists of reacting an aromatic amine with an α,β-unsaturated carbonyl compound (**Scheme 5**) in an acidic medium in the presence of an oxidizing agent [38, 39].



Scheme 5: Edification of tricycle1,10-phenanthrolinone by the Doebner-Von Miller method

2.4. Reaction from an ethoxymethylene malonic ester

This is a condensation reaction between 8-aminoquinoline and an ethoxymethylene malonic ester. It leads to an intermediate of type [(quinoline 8-ylamino) methylene] alkyl malonate. The latter is then cyclized under various conditions to lead to a 1,10-phenanthrolin-4(1H)-one ring (**Scheme 6**) bearing an alkyl carboxylate function in position 3 [40, 41].



Scheme 6: Edification of the tricycle1,10-phenanthrolin-4(1H)-on

3. Therapeutic potentiality of functionalized 1,10-phenanthroline derivatives

In this part of our study we will focus only on the therapeutic properties of 1,10-phenanthroline derivatives without added metal complexes. These different properties are declined in antimalarial, antibacterial, antitubercular, antifibrotic activities etc.

3.1. Antimalarial activities

Malaria remains the most widespread and deadly tropical parasitosis in the world. Malaria is a potentially fatal disease caused by parasites transmitted to people through the bites of infected female Anopheles mosquitoes. Malaria is preventable and potentially curable [42]. In 2019, WHO estimated 229 million malaria cases worldwide with 409,000 deaths. Children under five years of age are the most vulnerable group affected by malaria; in 2019, they accounted for 67% of malaria deaths worldwide (274,000) [43]. Malaria eradication efforts have resulted in a reduction in malaria incidence rates globally and in sub-Saharan Africa [44]. However, this eradication progress remains fragile, due to the development of pharmacoresistance to antimalarial drugs and insecticides, including artemisinin derivatives [45-47]. Faced with such a situation, the search for new and more efficient pharmacophores for Plasmodium becomes an urgent need. It is in this context that Yapi and associates have conceptualized and synthesized diazaphenanthrene analogues of halofantrine [48]. Indeed, halofantrine, although effective against chloroquine-resistant *Plasmodium falciparum* strains, has been withdrawn from the therapeutic arsenal because of its serious adverse effects such as ventricular arrhythmias [49]. The results of their work showed that compounds with the 1,10-phenanthroline base unit (**Figure 2**) were active on both chloroquine-resistant strains (FcB1-Columbia) and chloroquine-sensitive strains (Nigeria) with an IC_{50} of about 0.13 µM. Moreover, this activity was optimized by *N*-alkylation and salification of phenanthroline in mice infected with *Plamodium* vinckei petteri with ED_{50} of 7.86 mg/kg/day [50, 51].

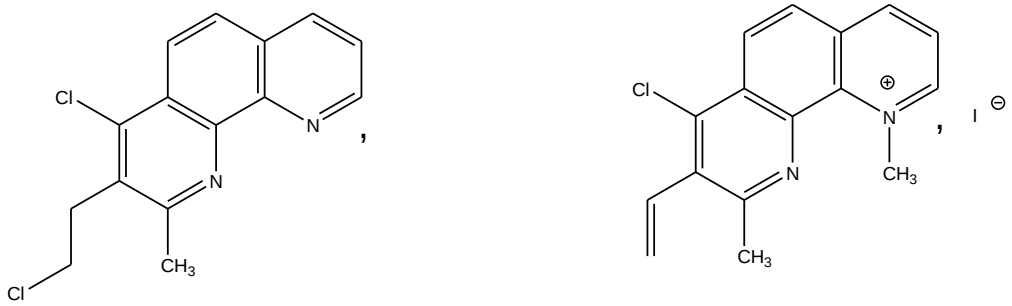


Figure 2: Chemical structures of antimalarial N-alkylated 1,10-phenanthroline derivatives

Building on the previous work, Mutofa and collaborators also synthesized *N*-alkylated and *N*-benzylated 1,10-phenanthroline derivatives with antiplasmodial potentialities. Among their derivatives, the $_N$-benzylated 1,10-phenanthroline compound (**Figure 3**) showed excellent antiplasmodial activity with an IC_{50} between 2.41 and 0.07 µM [52, 53]

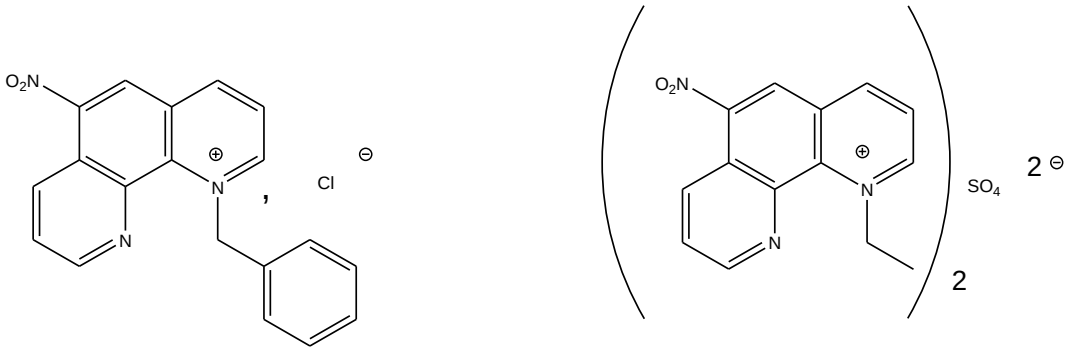


Figure 3: Chemical structures of N-alkylated and N-benzylated 6-nitro 1,10-phenanthroline antimalarial derivatives.

In addition, Sall and collaborators have synthesized a series of 1,10-phenanthroline conformational analogues of primaquine. These showed significant antiplasmodial activities in vitro on different strains of Plasmodium falciparum. Moreover, the compounds possessing a methoxyl group, like primaquine, proved to be more active than the latter. In addition, compound 5 (**Figure 4**) showed good gametocytocidal activity in vitro compared to primaquine [54].

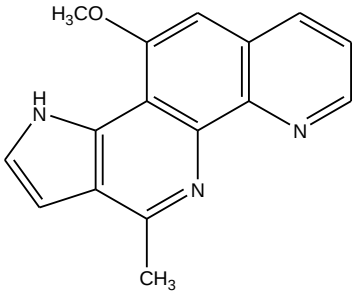
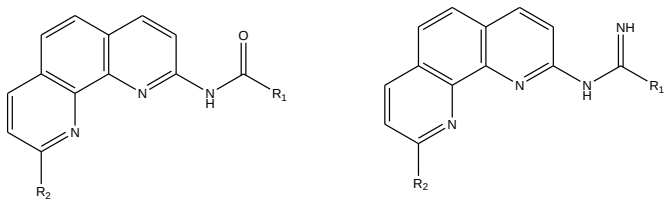


Figure 4: Chemical structure of compound 5 derived from 1,10-phenanthroline, conformational analogue of primaquine.

3.2. Antitubercular activities

Pulmonary tuberculosis represents the first cause of mortality of infectious origin in the world [55]. It is caused by a bacillus, in this case *Mycobacterium tuberculosis*. The therapeutic management of this disease is complicated not only by the long duration of treatment but also by the drug resistance of the bacilli to most drugs. To cope with this, a synergistic combination of several antituberculosis drugs has been proposed as a means of control [56-58]. However, with the emergence of multidrug-resistant or even ultra-resistant strains, the search for new and more effective molecules is essential. The first anti-tuberculosis investigations in the chemical series of 1,10-phenanthrolines were reported in 1991 by De Zwart and colleagues [59]. He synthesized and evaluated the anti-infective activities of 1,10-phenanthroline benzamide, 1,10-phenanthroline benzamidine and 1,10-phenanthroline aminobenzyole derivatives (**Figure 5**). The results obtained reveal that the said derivatives have activity against mycobacteria, protozoa (*Trichomonas*), fungi (*Candida albicans*) and bacteria responsible for pleuropneumonia such as mycoplasma. Moreover, the anti-infectious activities of its derivatives are improved in some cases by the addition of very small, non-toxic quantities of transition metals (Copper). In addition, the anti-tuberculosis activity of its compounds was significantly higher than that of rifampicin used as a reference drug [59].



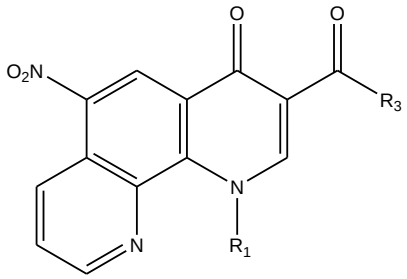
R_2 =H,halogen,alkyl,alkoxy,aromatic group, aliphatic carboxamid group
R_1= H,halogen, alkox, aromatic groupy, phenyl substituted, cycloalkyl, aromatic group

Figure 5: General chemical profile of 1,10-phenanthroline benzamide, 1,10-phenanthroline benzamidine and 1,10-phenanthroline aminobenzyole derivatives with antitubercular, antiprotozoal and anticandidosic activities

In 2009, Anshika et al showed that unsubstituted 1,10-phenanthroline exhibited in vitro antitubercular activity by inhibiting peptide deformylase, an enzyme essential for the maturation of bacterial growth and survival proteins. In addition, 1,10-phenanthroline has a synergistic action with major anti-tuberculosis drugs such as isoniazid and rifampicin [60]. Furthermore, Kidwai and colleagues evaluated the antibacillary activities of 5-nitro 1,10-phenanthroline (**Figure 6**) on *Mycobacterium tuberculosis*. Their study revealed that this compound inhibited the growth of Mycobacterium tuberculosis with an MIC_{99} at 0.5 µg/mL. The structure-activity relationship studies undertaken revealed that the nitro group was essential for the development of good antituberculosis activities. Furthermore, 5-nitro 1,10-phenanthroline appears to have a dual mechanism of action on Mycobacterium tuberculosis [61].

Figure 6: Chemical structure of 5-nitro 1,10-phenanthroline derivatives with antitubercular activities

More recently, Coulibaly and colleagues reported the excellent antitubercular activities of some 6-nitro derivatives of 1,10-phenanthrolinone (**Figure 7**) with MIC90s between 0.31 and 9.84 µM. The antitubercular activities of the 6-nitrophenantrolinones were retained on various mycobacterial species and some fluoroquinolone-resistant mutant strains. Furthermore, 6-nitro-phenanthrolinones were found to be nontoxic on Vero cells with IC_{50} > 100 µg/mL, which is 16 to 64 times their MICs [62].



R_1= CH_3, C_2H_5
R_3= OC_2H_5, OH, $NHNH_2$

Figure 7: General chemical profile of 6-nitro 1,10-phenanthrolinone derivatives with antitubercular activities

3.3. Antibacterial activities

Antimicrobial resistance is a growing health threat and compromises development. This resistance is favored by the generalized use or even abuse of certain antibiotics, in preventive or curative treatment in human and veterinary medicine [63]. Indeed, the excessive use of antibacterials has contributed to the elimination of sensitive bacteria and the selection of the most resistant. This selection pressure has led to the development of populations of antibiotic-resistant microorganisms and to a general decrease in the efficacy of antibiotics, ultimately leading to a therapeutic impasse [64]. Unfortunately, this antibiotic resistance affects almost all classes of antibiotics and we are witnessing the rapid emergence of multi-resistant pathogenic bacteria in hospitals, thus increasing the mortality and morbidity rates due to nosocomial infections for lack of effective treatment [65]. Faced with this situation, the development of new effective antibacterials, capable of bypassing the phenomena of drug resistance induced by the bacteria, is becoming an emergency. To address the need for new antibacterials, Lee and colleagues prepared and evaluated the antibacterial activities of 1,10-phenanthrolinone derivatives (**Figure 8**) on Gram-positive (*Staphylococcus aureus, Micrococcus luteus*) and Gram-negative (*Pseudomonas aeruginosa, Salmonella typhimurium*) bacteria. These presented antibacterial activities that were similar or even superior to those of Nalidixic acid used as reference drugs [40, 41].

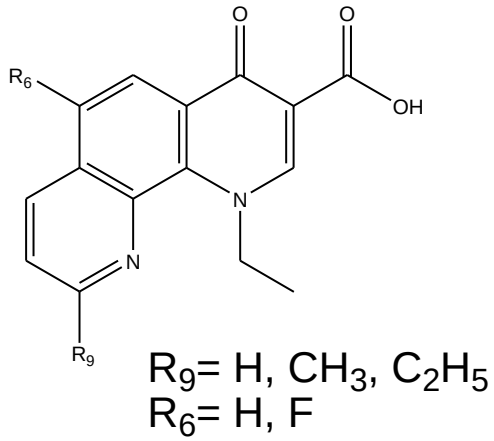


Figure 8: Chemical structures of 1,10-phenanthrolinone derivatives with antibacterial activities described by Lee.

More recently in 2020, the antibacterial activities of imidazo-1,10-phenanthroline derivatives were reported by Aslıhan and colleagues [66]. These showed that the antibacterial activities were influenced by the nature of the substituents on the phenyl ring directly linked to imadazole. Compound 3 substituted (**Figure 9**) with a chloroquinoline at this phenyl showed the best antibacterial activity with a Minimum Inhibitory Concentration at 156.25 µM.

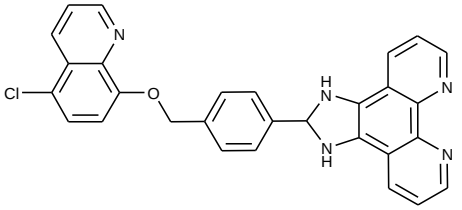


Figure 9: Chemical structure of compound 3 derived from imidazo-1,10-phenanthroline with antibacterial activities

3.4. Anticancer activities

According to the WHO, the word "cancer" is a generic term for a large group of diseases that can affect any part of the body. It is also referred to as malignant tumors or neoplasms. A characteristic feature of cancer is the rapid multiplication of abnormal cells with unusual growth, which can invade neighboring parts of the body and then migrate to other organs. This is known as metastasis and is the leading cause of death from cancer. Cancer is the second leading cause of death in the world, with approximately 10 million deaths per year, that is to say one in six

deaths is due to cancer worldwide [67]. Moreover, 70% of cancer deaths occur in low- and middle-income countries. As for anticancer treatment, it poses several problems such as toxicity, drug resistance and adverse effects [67, 68]. The chemical profile of 1,10-phenanthroline, due to its ability to intercalate with DNA bases, is a privileged reason for the development of anticancer drugs. Thus, several authors have reported in the literature the antitumor properties of 1,10-phenanthroline derivatives. The in vitro anticancer activities of 11 benzyl-1,10-phenanthroline derivatives on three human cancer cell lines, namely cervical cancer (HeLa), myeloma (NS-1) and breast cancer (MCF-7) have been reported by Eti Nurwening and colleagues. Their results show that (1)-N-(4-butoxybenzyl)-1,10-phenanthrolinium bromide (**Figure 10**) exhibited the best in vitro anticancer activity with an IC50 of 27.60 ± 2.76 µM on HeLa, 6.42 ± 5.53 µM on NS-1 and 9.44 ± 2.17 µM on MCF-7 cell lines [69].

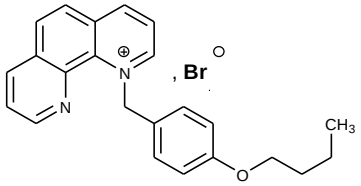


Figure 10: Chemical structure of (1)-N-(4-butoxybenzyl)-1,10-phenanthrolinium bromide with anti-cancer activity

In 2016, the antitumor activities of 2,9-di- sec -butyl-1,10-phenanthroline derivative on lung, head and neck cancer cell lines were reported. These showed that the 2,9-di- sec -butyl-1,10-phenanthroline derivative alone induced autophagy, G1 cell cycle arrest and apoptosis with CI_{50} between 0.1 and 0.2 M. Moreover, the 2,9-di- sec -butyl-1,10-phenanthroline derivative exhibited synergistic action with cisplatin without major toxicity [70].

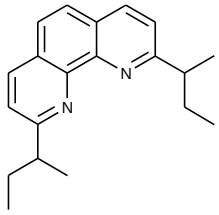


Figure 11: Chemical structure of 2,9-di-sec-butyl-1,10-phenanthroline derivative with anticancer activity

Recently in 2020, the anticancer activities of 2-(1,10-phenanthrolin-5-yl)imino)methyl)-5-bromophenol and *N*-(1,10-phenanthrolin-5-yl)- 1-(thiophen-3-yl)methanimine (**Figure 12**) against breast, cervical, colorectal, and prostate cancer cell lines as well as immortalized human keratinocytes have been reported. These compounds possess dose-dependent selective cytotoxicity on cancer cells, without major toxicity on normal cell lines [71].

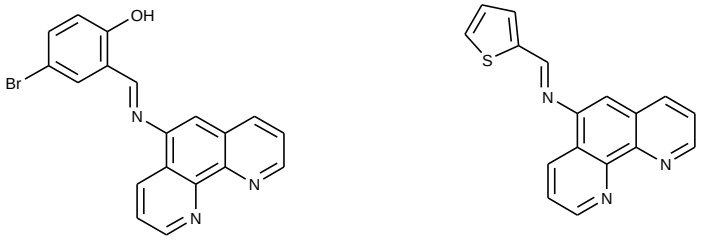


Figure 12: Chemical structure of 2-(1,10-phenanthrolin-5-yl)imino)methyl)-5-bromophenol and N-(1,10-phenanthrolin-5-yl)- 1-(thiophen-3-yl)methanimine derivatives with anticancer activities

3.5. Antifibrotic activities

Fibrosis is an elementary lesion of the connective tissue defined by the increase of fibrillar constituents of the extracellular matrix in a tissue or organ. It is a frequent component of inflammatory processes but can also occur in other pathological conditions (vascular, metabolic, tumor pathologies) [72]. The anti-fibroproliferative activities of polyfunctionalized 1,10-phenanthroline derivatives (**Figure 13**) were reported in a patent in 1999 [18]. In this patent the authors reported the inhibitory properties of 1,10-phenanthroline derivatives of the enzyme prolyl 4-hydroxylase involved in the hydroxylation of proline residues in collagen protein. The 4-hydroxyproline residues are essential for

the formation of the triple helix of collagen secreted in the fibrous tissue. Any compound capable of inhibiting prolyl 4-hydroxylase activity may be of potential value in the treatment of fibroproliferative disease such as rheumatoid arthritis, chronic arthritis, osteoarthritis, hepatic fibrosis, hepatic cirrhosis, pulmonary fibrosis, renal fibrosis, cardiac fibrosis, arteriosclerosis-associated fibrosis, and scar tissue formation after injury or surgery [73].

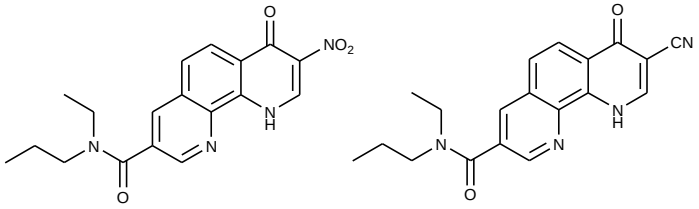


Figure 13: Chemical structure of some 1,10-phenanthrolinone derivatives with antifibrotic activities

3.6. Insecticidal activities

Porphyrin insecticides are chemical compounds that modulate the porphyrin-heme biosynthetic pathway. When these compounds are used alone or in combination with δ-aminolevulinic acid, they promote the accumulation of protoporphyrin IX in the insect. The uncontrolled biosynthesis of protoporphyrin causes the death of the treated insect in the dark and in the light [74]. Derivatives of 1,10-phenanthrolines have shown insecticidal activities on various insect vectors of diseases and pests of plant crops [75]. Thus, methylated derivatives of 1,10-phenanthroline (4-methylated, 5-methylated, 5,6-dimethylated, 4,7-dimethylated derivative), 5-chloro 1,10-phenanthroline and 5-nitro 1,10-phenanthroline (**Figure 14**) exhibited excellent insecticidal activities against *Trichoplusiani* with a minimum inhibitory concentration at 3 mM in the presence of 4 mM δ-aminolevulinic acid [76].

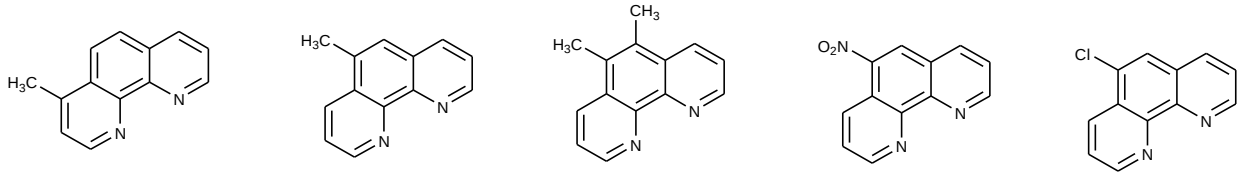


Figure 14: Chemical structure of some 1,10-phenanthrolinone derivatives with insecticidal activities

4. Conclusion

The 1,10-phenanthroline ring is a diazotized heterocycle with many pharmacological properties. Unfortunately, the high affinity of this chemical motif towards human metalloproteins is at the origin of a certain toxicity. To overcome this toxicity, the first strategy adopted was to form metal complexes with the nitrogen atoms at positions 1,10 of phenanthroline. The second strategy focused on functionalizing the 1,10-phenanthroline tricycle to reduce toxicity without further addition of metals. A number of variously functionalized 1,10-phenanthroline derivatives have shown excellent antitubercular, antifibrofilative activities and have been patented. This review is a contribution to the identification of the therapeutic potential of non-metal coupled 1,10-phenanthroline derivatives. It reveals that it is possible to functionalize 1,10-phenanthroline derivatives in order to reduce the toxicity of these derivatives while maintaining their therapeutic activities.

Conflict of Interest

The authors declare no conflict of interest as regards this work.

References

[1]. Gil, A., Melle-Franco, M., Branchadell, V. Calhorda, M. J. (2015). How the intercalation of phenanthroline affects the structure, energetics, and bond properties of DNA base pairs: theoretical study applied to adenine-thymine and guanine-cytosine tetramers. *Journal of chemical theory and computation*, 11(6): 2714–2728

[2]. Sánchez-González, A. and Gil, A. (2021). Elucidating the intercalation of methylated 1,10- phenanthroline with DNA: the important weight of the CH/H interactions and the selectivity of CH/p and CH/n interactions. *RSC-advances*, 11 (3): 1553-1563.

[3]. Gaetano, M., Gaia, G., Angela, L., Glauco. P., Silvia, B., Carol, I., Maria, P. C., Domenico D. (2019). The 1,10-Phenanthroline Ligand Enhances the Antiproliferative Activity of DNA-Intercalating Thiourea-Pd(II) and -Pt(II) Complexes Against Cisplatin-Sensitive and -Resistant Human Ovarian Cancer Cell Lines. *International Journal of Molecular Sciences*, 20(24:6122.

[4]. Voordouw, G., Milo, C., Roche, R. S. (1976). The determination of the binding constant of metalloenzymes for their active site metal ion from ligand inhibition data. Theoretical analysis and application to the inhibition of thermolysin by 1,10-phenanthroline. *Analytical biochemistry*, 70(2):313–326

[5]. Ellis, T. R., Crawford, B. D. (2016). Experimental Dissection of Metalloproteinase Inhibition-Mediated and Toxic Effects of Phenanthroline on Zebrafish Development. *International journal of molecular sciences*, 17(9):1503.

[6]. Day, T. A., Chen, G. Z. (1998). The metalloprotease inhibitor 1,10-phenanthroline affects Schistosoma mansoni motor activity, egg laying and viability. *Parasitology*, 116 (Pt 4): 319–325.

[7]. Andrea, B., Vito, L. (2010). 1,10-Phenanthroline: A versatile building block for the construction of ligands for various purposes. *Coordination Chemistry Reviews.* 17-18(254):2096-2180.

[8]. BriÑez-Ortega, E., Almeida, V. L., Lopes, J., Burgos, A. E. (2020). Partial inclusion of bis(1,10-phenanthroline)silver(I) salicylate in β-cyclodextrin: Spectroscopic characterization, in vitro and in silico antimicrobial evaluation. *Anais da Academia Brasileira de Ciencias*, 92(3):e20181323.

[9]. Backman-Blanco, G., Valdés, H., Ramírez-Apan, M. T., Cano-Sanchez, P., Hernandez-Ortega, S., Orjuela, A. L., Alí-Torres, J., Flores-Gaspar, A., Reyes-Martínez, R., Morales-Morales, D. (2020). Synthesis of Pt(II) complexes of the type [Pt(1,10-phenanthroline)(SArFn)2] (SArFn = SC6H3-3,4-F2; SC6F4-4-H; SC6F5). Preliminary evaluation of their in vitro anticancer activity. *Journal of Inorganic Biochemistry*, 211:111206

[10]. Upadhyay, A., Gautam, S., Ramu, V., Kondaiah, P., Chakravarty, A. R., (2019). Photocytotoxic cancer cell-targeting platinum(ii) complexes of glucose-appended curcumin and biotinylated 1,10-phenanthroline. *Dalton transactions*, 48(47):17556–17565.

[11]. Matos, C. P., Adiguzel, Z., Yildizhan, Y., Cevatemre, B., Onder, T. B., Cevik, O., Nunes, P., Ferreira, L. P., Carvalho, M. D., Campos, D. L., Pavan, F. R., Pessoa, J. C., Garcia, M. H., Tomaz, A. I., Correia, I., Acilan, C. (2019). May iron(III) complexes containing phenanthroline derivatives as ligands be prospective anticancer agents?. *European journal of medicinal chemistry*, 176:492–512.

[12]. AL Geoffrey. John Wiley & Sons (2013).

[13]. Satyanarayana, S., Dabrowiak, J. C., Chaires, J. B. (1993). Tris(phenanthroline)ruthenium(II) enantiomer interactions with DNA: mode and specificity of binding. *Biochemistry*, 32(10):2573–2584

[14]. Iganor, L., Howe, O., McCarron, P., McCann, M., Devereux, M. (2017). The Antibacterial Activity of Metal Complexes Containing 1,10- phenanthroline: Potential as Alternative Therapeutics in the Era of Antibiotic Resistance. *Current topics in medicinal chemistry*, 17(11):1280–1302.

[15]. McCarron, P., McCann, M., Devereux, M., Kavanagh, K., Skerry, C., Karakousis, P. C., Aor, A. C., Mello, T. P., Santos, A., Campos, D. L., Pavan, F. R. (2018). Unprecedented in Vitro Antitubercular Activitiy of Manganese(II) Complexes Containing 1,10-Phenanthroline and Dicarboxylate Ligands: Increased Activity, Superior Selectivity, and Lower Toxicity in Comparison to Their Copper(II) Analogs. *Frontiers in microbiology*, 9: 1432.

[16]. Gandra, R. M., Mc Carron, P., Fernandes, M. F., Ramos, L. S., Mello, T. P., Aor, A. C., Branquinha, M. H., McCann, M., Devereux, M., Santos, A. (2017). Antifungal Potential of Copper(II), Manganese(II) and Silver(I) 1,10-Phenanthroline Chelates Against Multidrug-Resistant Fungal Species Forming the Candida haemulonii Complex: Impact on the Planktonic and Biofilm Lifestyles. *Frontiers in microbiology*, 8: 1257.

[17]. Prashanthi, Y., Kiranmai, K., Ira, K. S. K., Chityala, V. K., Shivaraj (2012). Spectroscopic Characterization and Biological Activity of Mixed Ligand Complexes of Ni(II) with 1,10-Phenanthroline and Heterocyclic Schiff Bases. *Bioinorganic chemistry and applications*, 2012: 948534.

[18]. Gaëlle, D. S. Y., Yufanyi, D. M., Jagan, R., Agwara, M. O. (2016).Synthesis, characterization and antimicrobial properties of cobalt(II) and cobalt(III) complexes derived from 1,10-phenanthroline with nitrate and azide co-ligands. *Cogent Chemistry*; 2(1) :1253201

[19]. Vargas Rigo, G., Petro-Silveira, B., Devereux, M., McCann, M., Souza Dos Santos, A. L., Tasca, T. (2019). Anti-Trichomonas vaginalis activity of 1,10-phenanthroline-5,6-dione-based metallodrugs and synergistic effect with metronidazole. Parasitology, 146(9), 1179–1183.

[20]. Fernanda, M., Marston, T. B. (1945). The search for superior drugs for tropical diseases. II. Synthetic studies in the quinoline and phenanthroline series. Skraup and Conrad-Limpach-Knorr reactions. *The Journal of Organic Chemistry*, 10(4): 347-365.

[21]. Kaufmann, A., Radojevic, R. (1909). Über das p-Phenanthrolin. *Berichte der Deutschen Chemischen Gesellschaft*,42(2): 2612-2622

[22]. Gerdeissen G. H. (1889). Untersuchung des Metaamidochinaldins*Berichte der Deutschen Chemischen Gesellschaft*, 22 (1): 244-254

[23]. Skraup, Z. H. (1880). EineSynthese des Chinolins, *Berichte*,13: 2086

[24]. Manske, R. H. F. (1942). The Chemistry of Quinolines. *Chemical Reviews*, 30:113

[25]. Manske, R. H., Kulka, M. (2004). The Skraup Synthesis of Quinolines. *Organic Reactions, 7*: 59-98.

[26]. Blau, F. (1898). Überneueorganische Metallverbindungen. *Monatsheftefür Chemie und verwandte Teileanderer Wissenschaften*, *19*(1): 647-689.

[27]. Hans, G., Ernst, H. (1952). Fungistatic preparations US patent. US2617753A

[28]. W. Hieber and F Mühlbauer. Berichte der deutschenchemischen Gesellschaft (A and B Series), 61(9) (1928) 2149-2153.

[29]. Breckenridge, J. G., Singer, S. A. (1947). The preparation of 1,10-phenanthroline from o-phenylenediamine. *Canadian journal of research*, *25*(6 Sec B): 583.

[30]. Cai, L., Zhao, H., Zhang, W., Dai, L. (2010). A one-step synthesis method of 1,10-phenanthroline derivative. Patent. WO/2010/127574

[31]. Tartarini, G., Samaja, T. (1933). separazione e purificazione di basiorganichemediante la formazione di metallamine : o fenantrolina. *Annali di chimicaapplicata*., 23(351): 3279-3281.

[32]. Case, F. H. (1949). Substituted 1, 10-Phenanthrolines. II. Di-and Tri-methyl Phenanthrolines Related to 5-Methyl-1, 10-phenanthroline. *Journal of the American Chemical Society*, *71*(3), 821-823.

[33]. Koft, E., Case, F. H. (1962). Substituted 1, 10-Phenanthrolines, XII. Benzo and Pyrido Derivatives1. *The Journal of Organic Chemistry*, *27*(3), 865-868.

[34]. Case, F. H. (1948). Substituted 1, 10-Phenanthrolines. I. The Synthesis of Certain Mono-and Polymethyl-1, 10-phenanthrolines1. *Journal of the American Chemical Society*, *70*(12), 3994-3996.

[35]. Misani, F., Bogert, M. T. (1945). The search for superior drugs for tropical diseases. II. Synthetic studies in the quinoline and phenanthroline series. Skraup and Conrad-Limpach-Knorr reactions. *The Journal of Organic Chemistry*, *10*(4), 347-365.

[36]. Kuczyński, H., Sucharda; E., Surmiński, A. (1936). O reakcji 1- i 2-nitronaftalenu oraz 1,5-dwunitro-naftalenu z glicerynąikwasemsolnym. *RocznikiChemii*, 16(513):510-512.

[37]. Chen, Y., Han, K. Y., Liu, Y. (2007). Effective switch-on fluorescence sensing of zinc (II) ion by 8-aminoquinolino-β-cyclodextrin/adamantine acetic acid system in water. *Bioorganic & medicinal chemistry*, 15(13):4537-4542.

[38]. Doebner, O., Miller, W. (1881). Uebereine dem Chinolinhomologe Base. *Berichte der deutschenchemischen Gesellschaft*, 14(2):2812-2817.

[39]. Lüdtke, C., Haupt, A., Wozniak, M., Kulak, N. (2017). Synthesis of fluorine-containing 1, 10-phenanthrolines using mild versions of Skraup and Doebner-von Miller reactions. *Journal of Fluorine Chemistry*, 193: 98-105.

[40]. Jae, K. L., Sang, H. L., Sha, J. C. (1992). New Quinolones (Ⅰ); Synthesis of New Pyrido [3, 2-h] quinoline Derivatives and Their Antibacterial Activities. *Bulletin of the Korean Chemical Society*, 13(5):571-573.

[41]. Jae, K. L., Sang, H. L., Sha, J. C. (1994). Quinolone (II): synthesis of Fluoro-substituedpyrido[3,2- h] quinolone derivatives as potential antibacterials. *Korean Journal of Medicinal Chemistry*, 4(2): 92-100.

[42]. Talapko, J., Škrlec, I., Alebić, T., Jukić, M., Včev, A. (2019). Malaria: the past and the present. *Microorganisms*, *7*(6): 179.

[43]. World Health Organization. [consulted on October 18, 2021]. Accessible to https://www.who.int/fr/news-room/fact-sheets/detail/malaria

[44]. World Health Organization. [consulted on October 18, 2021]. Accessible to https://www.who.int/publications-detail-redirect/9789240015791

[45]. Shibeshi, M. A., Kifle, Z. D., Atnafie, S. A. (2020). Antimalarial drug resistance and novel targets for antimalarial drug discovery. *Infection and Drug Resistance*, 13:4047.

[46]. Cui, L., Mharakurwa, S., Ndiaye, D., Rathod, P. K., Rosenthal, P. J. (2015). Antimalarial drug resistance: literature review and activities and findings of the ICEMR network. *The American journal of tropical medicine and hygiene*, 93(3 Suppl): 57.

[47]. Fairhurst, R. M., Dondorp, A. M. (2016). Artemisinin-resistant Plasmodium falciparum malaria. *Microbiology spectrum*, 4(3):4-3.

[48]. Yapi, A. D., Mustofa, M., Valentin, A., Chavignon, O., TEULADE, J. C., Mallie, M., Blache, Y. (2000). New potential antimalarial agents: synthesis and biological activities of original diaza-analogs of phenanthrene. *Chemical and pharmaceutical bulletin*, 48(12) :1886-1889.

[49]. Bouchaud, O., Imbert, P., Touze, J. E., Dodoo, A. N., Danis, M., Legros, F. (2009). Fatal cardiotoxicity related to halofantrine: a review based on a worldwide safety data base. *Malaria Journal*, 8(1):1-8.

[50]. AD Yapi, A Valentin, JM Chezal and Al. Yapi, A. D., Valentin, A., Chezal, J. M., Chavignon, O., Chaillot, B., Gerhardt, R., Blache, Y. (2006). In Vitro and in Vivo Antimalarial Activity of Derivatives of 1, 10-Phenanthroline Framework. *Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry*, 339(4):201-206.

[51]. Yapi, A. D., Desbois, N., Chezal, J. M., Chavignon, O., Teulade, J. C., Valentin, A., Blache, Y. (2010). Design and preparation of aza-analogues of benzo [c] phenanthridine framework with cytotoxic and antiplasmodial activities. *European journal of medicinal chemistry*, 45(7):2854-2859.

[52]. Hadanu, R., Mastjeh, S., Jumina, J., Mustofa, M., Sholikhah, E. N., Wijayanti, M. A. (2012). Synthesis and antiplasmodial activity testing of (1)-N-alkyl-and (1)-N-benzyl-6-nitro-1, 10-phenanthrolinium salts as new potential antimalarial agents. *Indonesian Journal of Chemistry*, 12(2): 152-162.

[53]. Hadanu, R., Mastjeh, S., Jumina, J., Mustofa, M., Widjayanti, M. A., Sholikhah, E. N. (2010). Synthesis and antiplasmodial activity testing of (1)-N-(4-methoxybenzyl)-1, 10-phenanthrolinium bromide. *Indonesian Journal of Chemistry*, 7(2): 197-201.

[54]. Sall, C., Yapi, A. D., Desbois, N., Chevalley, S., Chezal, J. M., Tan, K., Blache, Y. (2008). Design, synthesis, and biological activities of conformationally restricted analogs of primaquine with a 1, 10-phenanthroline framework. *Bioorganic & medicinal chemistry letters*, 18(16): 4666-4669.

[55]. Horsburgh Jr, C. R., Barry III, C. E., Lange, C. (2015). Treatment of tuberculosis. *New England Journal of Medicine*, 373(22): 2149-2160.

[56]. Rabahi, M. F., Silva Júnior, J., Ferreira, A., Tannus-Silva, D., Conde, M. B. (2017). Tuberculosis treatment. *Jornalbrasileiro de pneumologia: publicacaooficial da Sociedade Brasileira de Pneumologia e Tisilogia*, 43(6): 472–486.

[57]. Zumla, A., Chakaya, J., Centis, R., D'Ambrosio, L., Mwaba, P., Bates, M., Migliori, G. B. (2015). Tuberculosis treatment and management—an update on treatment regimens, trials, new drugs, and adjunct therapies. *The Lancet Respiratory Medicine*, 3(3): 220-234.

[58]. Pranger, A. D., Van Der Werf, T. S., Kosterink, J. G. W., Alffenaar, J. W. C. (2019). The role of fluoroquinolones in the treatment of tuberculosis in 2019. *Drugs*, 79(2): 161-171.

[59]. Zwart, H. D., Marcel, A., Van Der Goot, H., Timmerman, H. (1991). 1,10-phenanthroline derivatives. Patent WO1991005785A1.

[60]. Sharma, A., Sharma, S., Khuller, G. K., Kanwar, A. J. (2009). In vitro and ex vivo activity of peptide deformylase inhibitors against Mycobacterium tuberculosis H37Rv. *International journal of antimicrobial agents*, 34(3), 226-230.

[61]. Kidwai, S., Park, C. Y., Mawatwal, S., Tiwari, P., Jung, M. G., Gosain, T. P., Singh, R. (2017). Dual mechanism of action of 5-nitro-1, 10-phenanthroline against Mycobacterium tuberculosis. *Antimicrobial agents and chemotherapy*, 61(11): e00969-17.

[62]. Coulibaly, S., Cimino, M., Ouattara, M., Lecoutey, C., Buchieri, M. V., Alonso-Rodriguez, N., Dallemagne, P. (2020). Phenanthrolinic analogs of quinolones show antibacterial activity against M. tuberculosis. *European Journal of Medicinal Chemistry*, 207: 112821.

[63]. World Health Organization. [consulted on October 18, 2021]. Accessible to https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance

[64]. Oz, T., Guvenek, A., Yildiz, S., Karaboga, E., Tamer, Y. T., Mumcuyan, N., Ozan, V. B., Senturk, G. H., Cokol, M., Yeh, P., Toprak, E. (2014). Strength of selection pressure is an important parameter contributing to the complexity of antibiotic resistance evolution. *Molecular biology and evolution*, 31(9): 2387–2401.

[65]. Peterson, E., Kaur, P. (2018). Antibiotic Resistance Mechanisms in Bacteria: Relationships between Resistance Determinants of Antibiotic Producers, Environmental Bacteria, and Clinical Pathogens. *Frontiers in microbiology*, 9 : 2928.

[66]. Obalı, A. Y., Akçaalan, S., Arslan, E., Obalı, İ. (2020). Antibacterial activities and DNA-cleavage properties of novel fluorescent imidazo-phenanthroline derivatives. *Bioorganic chemistry*, 100: 103885.

[67]. World Health Organization. [consulted on October 18, 2021]. Accessible to https://www.who.int/fr/news-room/fact-sheets/detail/cancer

[68]. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, 68(6):394–424.

[69]. Sholikhah, E. N., Jumina, J., Widyarini, S., Hadanu, R., Mustofa, M. (2018). In vitro anticancer activity of N-benzyl 1, 10-phenanthroline derivatives on human cancer cell lines and their selectivity. *Indonesian Journal of Biotechnology*, 23(2):68-73.

[70]. Wang, D., Peng, S., Amin, A. R., Rahman, M. A., Nannapaneni, S., Liu, Y., Chen, Z. G. (2016). Antitumor Activity of 2, 9-Di-Sec-Butyl-1, 10-Phenanthroline. *PloS one*, 11(12): e0168450.

[71]. Prasad, K. S., Pillai, R. R., Shivamallu, C., Prasad, S. K., Jain, A. S., Pradeep, S., Syed, A. (2020). Tumoricidal Potential of Novel Amino-1, 10-phenanthroline Derived Imine Ligands: Chemical Preparation, Structure, and Biological Investigations. *Molecules*, 25(12): 2865.

[72]. Mack, M. (2018). Inflammation and fibrosis. *Matrix Biology*, 68: 106-121.

[73]. Philip, E. N., Neil, J. H., Huang, X., Michael, S., George, M.R. (1999). Phenanthroline derivatives. Patent WO1999021860 A1.

[74]. Rebeiz, C. A., Juvik, J. A., Rebeiz, C. C. (1988). Porphyric insecticides: 1. Concept and phenomenology. *Pesticide biochemistry and physiology*, 30(1):11-27.

[75]. Rebeiz, C. A., Gut, L. J., Lee, K., Juvik, J. A., Rebeiz, C. C., Bouton, C. E., Towers, G. H. N. (1995). Photodynamics of porphyric insecticides. *Critical reviews in plant sciences*, 14(4): 329-366.

[76]. Gut, L. J., Lee, K., Juvik, J. A., Rebeiz, C. C., Bouton, C. E., Rebeiz, C. A. (1993). Porphyric insecticides. IV: Structure-activity study of substituted phenanthrolines. *Pesticide science*, 39(1): 19-30.